REMARKS

Applicants have carefully considered this Application in connection with the Examiner's Office Action, and respectfully request reconsideration of this Application in view of the above amendments and the following remarks.

Claims 1-47 are pending in this application.

Claim 26 has been amended to correct a typographical error omitting the word "is."

Claims 11-13 and 29 have been amended to properly refer to "IPN nanoparticles."

I. Claim Rejections under 35 USC §112

The Examiner has rejected Claims 11-13 on the grounds that there is insufficient antecedent basis for the term "wherein the mono-disperse nanoparticles...", and Claim 29 on the grounds that there is insufficient antecedent basis for the term "...the mono-dispersed IPN...."

Applicants have amended Claims 11-13 to recite "wherein the IPN nanoparticles..." and Claim 29 has been amended to recite "...the IPN nanoparticles...." These claims are therefore proper and in condition for allowance.

II. Claim Rejections under 35 USC §102

Applicants wish to thank the Examiner for withdrawing the rejection of Claims 1-10 as being anticipated by the Kubota et al. (Journal of Applied Polymer Science, 2001, Vol. 80, p. 789-805, "the Kubota Reference").

The Examiner has rejected Claims 1, 4-10, and 13-14 under 35 USC §102(b) as being anticipated by Dhara et al. (Macromol Chem Phys 2001, Vol. 202, p.3617-3623, "the Dhara Reference"). The Examiner states that the Dhara Reference teaches an aqueous dispersion of hydrogel nanoparticles comprising interpenetrating polymer network nanoparticles wherein each

IPN nanoparticle comprises a first polymer network interpenetrating a second polymer network; and an aqueous medium, the first polymer comprises poly(-N-isopropylacrylamide) and the second polymer comprises poly(acrylic acid), the total polymer concentration is 2 wt%, the weight ratio is 2:1 (p. 3618, first column, second and third paragraphs). The Examiner states that the hydrogel can undergo a reversible gelation in response to a change in stimulus applied thereon, the stimulus is a change in temperature, and the temperature is about 34 °C (p. 8618, second column, second and third paragraphs).

Applicants respectfully disagree with the Examiner. The Dhara Reference does not teach IPN nanoparticles of hydrogel dispersed in water, but rather teaches a continuous sheet of hydrogel. The reference does not teach nanoparticles, and therefore cannot teach a dispersion of such nanoparticles in an aqueous medium. Moreover, the hydrogel taught in the Dhara Reference is produced by a method which does not produce nanoparticles, as described in detail below.

Page 3618, column 1, paragraph 3, of the Dhara Reference describes steps in a method for forming a hydrogel with an interpenetrating network of PNIPA and PAA. Although water is used in the preparation, the final product is a hydrogel, and not a dispersion of nanoparticles in an aqueous medium. This is emphasized by the sentence, "(t)he gelled slab was dislodged and cut into circular discs. The pieces were washed repeatedly with distilled water and dried at room temperature." It is therefore clear that the final product is not a liquid, but rather a solid. The current claims recite an aqueous dispersion of hydrogel nanoparticles, which could not be handled and washed as described in the reference.

Figure 16a of the current application shows a schematic diagram of the physically bonded nanoparticle network that is formed above the gelation temperature of the currently-claimed composition. In paragraph [0077] of the current specification, the structure of the hydrogel nanoparticles is described as follows. "There may be two types of pores created during the formation of an IPN nanoparticle network: one is large and encircled by many nanoparticles; the other is small and encircled by compact nearest neighboring particles as shown in Figure 16a. The size of the large pores is determined by the number of surrounding particles. Upon the decrease of the polymer concentration, both the size and the number of the large pores increases. On the other

hand, the size of the small pore is determined only by the particle size: the bigger the spherical building block, the larger the inter-particle pore. The initial burst release is due to the drug entrapped in the large pores while the slow, late release is due to the drug entrapped in the small pores."

This contrasts with the hydrogen-bonded networks which are described on p. 3618, first full paragraph, and shown in Figure 3 of the Dhara Reference.

The composition of the current claims comprises both hydrogel nanoparticles and aqueous medium, as is recited in Claim 1, and furthermore forms multiple types of pores when the hydrogel is heated above gelation temperature. Applicants submit that because of this difference, the Dhara Reference cannot be said to anticipate the current claims, and the claims are therefore novel and in condition for allowance.

III. Claim Rejections under 35 USC §103

The Examiner has rejected Claims 1-47 on the grounds that they are obvious over the Dhara Reference, in view of Gan and Lyon (J. Am. Chem. Soc., 2001, Vol. 123, No. 31, p. 7511-7517, "the Gan Reference"), Hennink and Nostrum (Advanced Drug Delivery, 2002, Vol. 13, p.13-36, "the Hennink Reference"), and in further view of the Kubota Reference.

Claims 1-14, and 41-47

The Examiner states that the Dhara Reference teaches an aqueous dispersion of hydrogel nanoparticles comprising interpenetrating polymer network nanoparticles, wherein each IPN nanoparticle comprises a first polymer network interpenetrating a second polymer network, and an aqueous medium; the first polymer comprises poly(-N-isopropylacrylamide) and the second polymer comprises poly(acrylic acid), the total polymer concentration is 2 wt%, and the weight ratio is 2:1 (p. 3618, first column, second and third paragraphs). The Examiner states that the hydrogel can undergo a reversible gelation in response to a change in stimulus applied thereon, the stimulus is a change in temperature, the temperature is about 34°C (p. 8618, second column, second and third paragraphs).

Applicants disagree with the Examiner's statement that the Dhara Reference teaches an aqueous dispersion of hydrogel nanoparticles. As described above, the Dhara Reference teaches a continuous sheet of hydrogel, rather than hydrogel nanoparticles. This can be seen on p. 3618, column 1, paragraph 3, which describes cutting the hydrogel into pieces and washing it with water. This clearly indicates that the composition of the Dhara Reference is a solid hydrogel, rather than an aqueous dispersion of hydrogel nanoparticles. This is also highlighted in Figure 3 of the Dhara Reference, which shows a continuous linkage between the polymer networks. In contrast, paragraph [0011] of the current specification recites "(t)he mono-disperse nanoparticles have a uniformed sized hydrodynamic radius that is in the range from about 75 nm to about 200 nm."

Therefore, there is no teaching in the Dhara Reference which would have suggested the aqueous dispersion of IPN hydrogel nanoparticles as recited in Claims 1-14 and 41-47. The Hennink Reference and the Kubota Reference are similarly lacking any description of hyrodgel nanoparticles.

The Gan Reference does teach hydrogel nanoparticles, however, the nanoparticles of the Gan Reference are core-shell hydrogel nanoparticles (see abstract, first line). These are distinct compositions from the compositions of Claims 1-14 and 41-47, which explicitly recite that "the IPN nanoparticles are substantially free of a shell and core polymer configuration...." The Gan Reference therefore fails to disclose a compositon with the structure or function of the currently-claimed composition.

The Examiner further states that the Kubota Reference teaches the application of stimuli and swelling-controlled hydrogels in drug delivery and the need for gels that can change the release rate of incorporated drugs according to stimuli. However, Applicants submit that teaching the need for a composition is not the same as teaching the composition which will meet that need. The statement by the authors in the Kubota Reference that "(a)pproaches such as stimuli-sensitive and swelling-controlled polymers have received much attention in current pharmaceutical research," and that available systems "are not suitable for a DDS [drug delivery system] that releases drugs in case of high body temperature," (see page 1028, second complete paragraph) indicate that this need has not been met, and that further research is required. If the technology for controlling the release rate of drugs incorporated in hydrogels had been precisely understood, then gels with the correct parameters

would have been readily found in the literature, and the authors of the Kubota Reference would not have expressed such a need.

Therefore, one of skill in the art who was familiar with the Dhara, Gan, Hannink, and Kubota References would have been lacking the suggestion or specific instructions for producing an aqueous dispersion of hydrogel nanoparticles substantially lacking core-shell configuration, for incorporating a biologically active agent into such a dispersion, and for modulating particle size in hydrogel nanoparticles which are lacking core-shell configuration. The development of these parameters is well outside the bounds of normal experimentation, requiring not only refinement of a multitude of parameters, but the inventive concepts of driving the swelling and size properties to a particular useful value.

Claims 15-40

The Examiner has rejected Claims 15-40, stating that Dhara et al. teach a method of preparing an IPN which would have rendered the present claims obvious. The Examiner further states that the Dhara Reference teaches a method of preparing an IPN comprising, providing a first mono-dispersed polymer nanoparticles prepared by mixing a first monomer, a first cross-linking agent, and a first initiator at a first temperature, adding to the first mono-dispersed polymer nanoparticles a second monomer, a second cross-linking agent, a second initiator and an activator, mixing the nanoparticles solution for a period of time at a second temperature, isolating the IPN nanoparticles, N,N'-methylelebisacrylamide (BIS), and potassium persulfate, poly(acrylic acid), ammonium persulfate, and TEMED, at about 21°C (ambient temperature) (p. 3618, first column, second and third paragraphs, and fifth paragraph).

First, as described in detail above, the method taught by Dhara relates to a solid hydrogel, rather than a method for producing an aqueous dispersion of hydrogel nanoparticles, which is recited in the current claims. The methods are aimed toward the production of distinct compositions.

The Examiner further states that, although the Dhara Reference does not teach hydrogel nanoparticles comprising a drug, the Gan Reference would have provided the information necessary for one of skill in the art to produce such a composition. As described in detail above, Gan does not provide such information, but rather discussed the desirability of producing such a composition.

The Examiner also states that the Gan Reference teaches controlling the size of hydrogel particles using SDS (a surfactant), and that such a method would have been applicable to producing hydrogel nanoparticles of a given size using the methods of the Dhara Reference. However, the Gan Reference teaches core-shell poly-N-isopropylacrylamide nanoparticles, while the current claims explicitly recite "substantially free from core-shell configuration." The distinction is clear on p. 7512, first full paragraph, of the reference, which describes the preparation of NIPA core particles and subsequent isolation of the core particles using dialysis, followed by addition of the shell. Because the particles described in the Gan Reference are fundamentally different from the particles recited in the current claims, there could be no expectation that the SDS of the Gan Reference would have the same effect on the currently-claimed composition.

The Examiner also states that the Kubota Reference teaches the application of stimuli and swelling-controlled hydrogels in drug delivery and the need for gels that can change the release rate of incorporated drugs according to the stimuli. As described in detail above, the method for accomplishing this is not taught by the Kubota Reference, only that it would be desirable to do so. Therefore, the Kubota Reference does not teach a method which would motivate one of skill in the art to practice the method described in the current claims.

The Examiner further states that, while the Dhara Reference does not teach the cross-linking agents EDAC and adipic acid dihydrazide, these reagents were being used in the art as cross-linking agents for hydrogel preparation as shown in the Hennink Reference. However, as discussed above, the Dhara Reference is sufficiently different from the currently-claimed method, that the optimal choice of cross-linking reagent would not have been obvious without experimentation.

Therefore, one of skill in the art who was familiar with the Dhara, Gan, Hannink, and Kubota References would have been lacking the suggestion or specific instructions for producing an aqueous dispersion of hydrogel nanoparticles substantially lacking core-shell configuration, for incorporating a biologically active agent into such a dispersion, and for modulating particle size in hydrogel nanoparticles which are lacking core-shell configuration. The development of these parameters is well outside the bounds of normal experimentation, requiring not only refinement of a multitude of

parameters, but the inventive concepts of driving the swelling and size properties to a particular useful value.

Applicants therefore submit that Claims 1-47 are nonobvious, and patentable under 35 USC §103.

IV. Conclusion

Applicants respectfully submit that, in light of the foregoing comments and amendments, all pending claims are now in condition for allowance. A Notice of Allowance is therefore requested.

If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,

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